American Journal of Transplantation 2002; 2: 898–903
Blackwell Munksgaard

ISSN 1600-6135

What's New – What's Hot

What's in the Pipeline? New Immunosuppressive Drugs in Transplantation

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In the pipeline, there are a number of novel immunosuppressive drugs in preclinical development or in early clinical trials. The major target of new agents are cell-surface molecules important in immune cell interactions (especially the costimulatory pathway), signaling pathways that activate T cells, T-cell proliferation and trafficking and recruitment of immune cells responsible for rejection. The most promising biologic agents include a humanized anti-CD11a (anti-LFA1), humanized anti-B7.1/B7.2, a second-generation CTLA4Ig (LEA29Y) and a humanized antibody to anti-CD45 RB. Inhibitors of T-cell activation and signaling are still in preclinical development. The most interesting inhibitors of T-cell proliferation include inhibitors of the Janus protein tyrosine kinase, JAK3, and FK778, a leflunomide analog. Chemokines play an important role in rejection by virtue of their critical role as regulator of trafficking and activation of lymphocytes. Early trials of FTY720, a synthetic small molecule with functional homology to sphingosine-1 phosphate leading to lymphocyte sequestration, appear very promising; however, enthusiasm for this drug is mitigated by its potential cardiac side-effects. Antagonists to several chemokine receptors, including CCR1, CXCR3 and CCR5, have been shown to be effective in experimental transplantation and are likely to be considered for clinical development.

Key words: Immunosuppression, monoclonal antibodies, transplantation

Received 21 May 2002, revised and accepted for publication 5 June 2002

Introduction

The past decade has witnessed important advances in transplantation in terms of therapeutic modalities and improved short-term and long-term outcomes. Impressive numbers of experimental drugs were brought to the clinic, had successful phase III trials and were approved for clinical use. Cyclosporine, the drug that ushered in the renaissance era of transplant therapeutics, was replaced by a microemulsion formulation with more predictable pharmacokinetics (1). A recent analysis showed that patients treated with the microemulsion cyclosporine formulation had better long-term graft outcome than patients treated with Sandimmune (2). A second calcineurin inhibitor, tacrolimus, was successfully introduced for both liver and renal transplantation (3,4). Two antiproliferative drugs, mycophenolate mofetil (MMF) and sirolimus, with different mechanisms of action were introduced in 1995 and 1999, respectively, and have had a dramatic effect on the reduction of the incidence of acute rejection in renal transplantation (5,6). There were also important advances in biologic induction therapies. A new generation of monoclonal antibodies (mAbs) targeting the α chain of the interleukin-2 receptor was shown in phase III trials to result in selective and effective immunosuppression with a safety profile unmatched by any other immunosuppression agent (7,8). Finally, the biologic depleting agent antithymocyte globulin (Thymoglobulin) that has been available in Europe for over a decade was finally approved in the United States for use in the treatment of steroid-resistant acute rejection (9). It has replaced OKT3 as the depleting antilymphocyte agent of choice for induction therapy, especially in high immunologic risk patients.

The drugs and biologic agents which will be introduced in the next decade will be propelled by the evolution of our understanding of the pathways that lead to rejection, tolerance, tissue repair, as well as by the ever-expanding genomic discoveries. Ironically, it will be several years before the next new drug will be approved for transplantation, as currently there are no phase III trials under way with new drugs or biologic agents. The success of the existing immunosuppression regimens may hinder future drug development because of the vanishing endpoint of acute rejection, and the challenge of demonstrating improvement in long-term outcome (10). Meanwhile, several unmet clinical needs persist. These include patients at high risk of rejection and graft loss, such as African Americans, patients with high panel-reactive antibodies, as well as patients who develop delayed graft function. Thus the thrust of future drug development is likely to result in immunosuppression therapy with a unique or novel mechanism of action that, while not necessarily resulting in superior short-term efficacy, will lack current drug toxicities and lead to better preservation of renal function. The promise of immunologic tolerance hovers on the horizon unfulfilled but not beyond reach, and convincing nonhuman primate models and the use of a combination of experimental drugs or biologic agents in clinical trials will be required for further progress. The recently established NIH-sponsored Immune

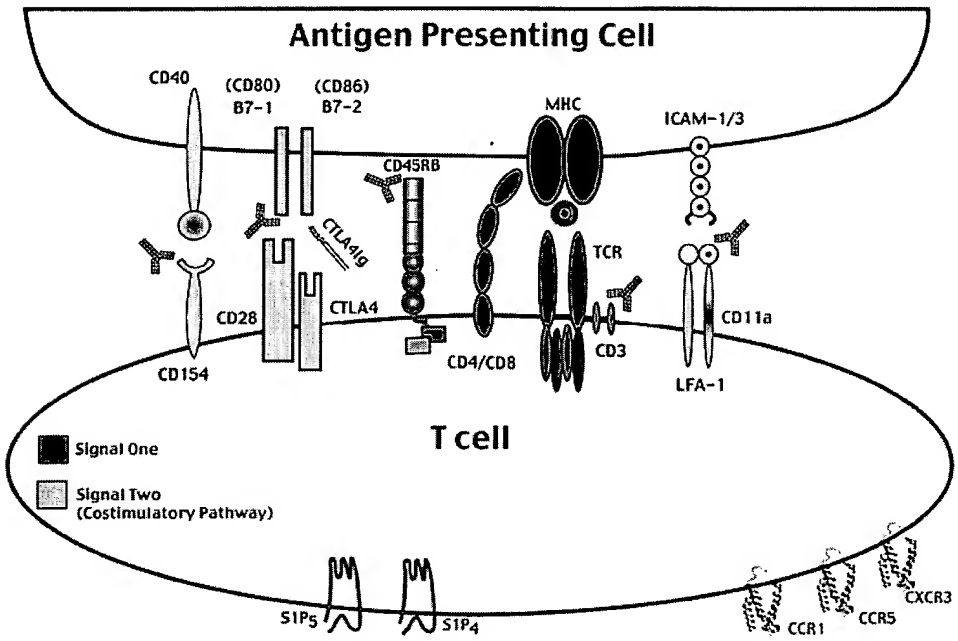

Figure 1: Cell-surface targets of biologic agents.

Tolerance Network will be an important catalyst in promoting clinical experimentation with tolerance-inducing regimens.

New Targets for Immunosuppression

Table 1 shows the major targets of new agents in immunosuppression in clinical and preclinical studies.

Interference with cell-surface molecules important in immune cell interactions

Targeting cell-surface molecules with biologic agents has several advantages over maintenance oral drug therapy. Cell-surface molecules can be readily blocked with monoclonal antibodies or receptor-fusion proteins, and are easily saturated and modulated. The new humanized biologic agents have the added advantage of a long half-life, requiring infrequent administration. In addition, there is a paradigm shift in biologic drug development from short-term induction therapy to chronic administration as a replacement for maintenance oral immunosuppression. The potential advantage of chronic biologic therapy is regimen simplification (monthly or bi-monthly administrations), no requirement for therapeutic drug monitoring, and assured compliance.Figure 1 shows some of the current biologic agents in early clinical trials or being considered for clinical development. Other biologic agents that are being used in single-center trials but are not yet part of a formal drug development program by their sponsor include campath 1H, a humanized anti-CD52 antibody that results in prolonged lymphocytes depletion; rituximab, an anti-CD20 monoclonal antibody that targets B cells; and several humanized mutagenized nonmitogenic anti-CD3 mAbs(11–16). Kirk et al. and Knechtle et al. are conducting single-center trials with campath 1H in combination with sirolimus in an attempt to induce long-term tolerance or at the very least drug minimization. Rituximab is being used off-label in patients with elevated levels of panel-reactive antibodies as well as in patients undergoing acute humoral rejection (13). The new generation of humanized anti-CD3 mAbs are engineered to loose their toxicities through amino acid(s) substitution in the Fc domain in order to reduce binding to Fc receptors. These antibodies include HuM291, Campath 3 and hOKT3γ1 (the humanized-mutagenized version of murine OKT3)(14–16). hOKT3γ1 is licensed to Centecor and is being considered for use in new trials in renal transplantation.

The most dramatic failure in the recent past is Biogen's anti-CD154 (hu5C8) (17). Despite impressive experimental evidence, the phase I trial with the humanized hu5C8 was halted following thromboembolic events, as well as failure of immunosuppression efficacy (5/7 patients had rejection episodes). IDEC Pharmaceutical has started clinical trials with another humanized anti-CD154, IDEC131 (targeting a different epitope than hu5C8) in patients with autoimmune diseases, but may extend these studies to organ transplantation

Table 1: Major targets of new agents in development

Interference with cell-surface molecules important in immune cell interactions
Inhibiting signaling mechanisms
Inhibiting T-cell proliferation
Alter trafficking and recruitment of immune cells responsible for rejection

pending results in nonhuman primates. It is clear that there is continuing interest in exploring disruption of the CD40 pathway in clinical trials.

A humanized antibody to CD45 (anti-CD45RB) may soon put the spotlight back on CD45 as an important drug target. CD45 was first described in 1978 as a family of glycoproteins expressed on the surface of nucleated hematopoietic cells (18). CD45 is a transmembrane protein tyrosine phosphatase involved in the coupling of signals from the T-cell receptor to the proximal signaling apparatus. Different CD45 isoforms generated by the alternative slicing of exons A, B and C are expressed by T cells with distinct functions. Monoclonal antibodies to the RB isoforms of CD45 have been shown to induce long-term survival and tolerance in various experimental models of solid organs and islet cell transplant(19–21). The mechanism of action of anti-CD45RB mAbs is unclear. However, it may modulate the expression of RB isoforms with different molecular weights (m.w.) (21). T cells with high m.w. CD45RB ($CD45RB^{bright}$ cells) secrete IL-2, while low m.w. CD45RB ($CD45RB^{dim}$ cells) secrete Il-4. Basadonna et al. showed that lymphocytes obtained from animals treated with anti-CD45RB showed decreased $CD45RB^{bright}$ cells and had up-regulation of $CD45RB^{dim}$ cells (19). In addition,*in vitro* effects of anti-CD45RB mAbs include down-regulation of theL-selectin, up-regulation of CTLA-4, and suppression of TH1 cytokine production. In a seminal study, Lazarovits et al. showed that an anti-CD45RB mAb in two doses resulted in long-term graft survival in murine renal allografts (20). Nonhuman primate models are currently underway in preparation for a phase I clinical trial in renal transplant recipients by Abgenix.

Efalizumab is a humanized IgG1 monoclonal antibody targeting the CD11a chain of LFA1. Efalizumab binds to LFA1, preventing LFA1–ICAM interaction. Direct blockade of ICAM-1 with a mAb failed to show any benefit in a randomized renal transplant trial, possibly due to redundancy in the ICAMs (22) Anti-CD11a has been shown to block T-cell adhesion, trafficking and activation (23). Pre-transplant therapy with anti-CD11a prolongs survival of murine skin and heart allografts, and monkey-heart allografts (24). Efalizumab has been successfully used in phase III trials in patients with psoriasis. In a phase I/II open label, dose ranging, multidose, multicenter trial, Efalizumab was administered subcutaneously, weekly for 12 weeks following renal transplantation (25).Table 2 shows patient enrollment as well as the maintenance immunosuppression. At 3 months, 3/38 patients (7.8%) had a reversible rejection episode and at 6 months there was one additional rejection for a cumulative rejection rate of 10.4%. Pharmacokinetic and pharmacodynamic studies showed that the lower doses of Efalizumab (0.5 mg/kg) produced saturation and 80% down-modulation of CD11a by 24–48 h following therapy. In a subset of 10 patients who received the high-dose Efalizumab (2 mg/kg) with full-dose cyclosporine and MMF, 3/10 patients developed post-transplant lymphoproliferative disease. Thus Efalizumab appears to be an effective immunosuppressive agent, but it is best used in a lower-dose regimen with less intense maintenance immunosuppression.

Table 2: Efalizumab dose and concomitant immunosuppression

Dose of Efalizumab	Group I 0.5 mg/kg	Group II 2.0 mg/kg
A: Half-dose CsA + sirolimus + prednisone	n = 9	n = 9
B: Full-dose CsA + MMF + prednisone	n = 10	n = 10
Totals (n = 38)	n = 19	n = 19

CsA, cyclosporine; MMF, mycophenolate mofetil.

The costimulatory pathway also referred to as signal two (signal one being the antigen-driven pathway via the T-cell receptor) is critical in triggering T-cell activation, proliferation and effector function(26–29). While many coactivation or costimulatory pathways have been described (CD154-CD40, LFA_1-ICAM-1, ICOS-B7RP-1) the CD28–B7 interaction remains the most thoroughly characterized and possibly represents the best target of immunosuppression therapy. Despite the failure of anti-CD154 in a single clinical trial, blocking CD28 interaction with B7 (either with CTLA4Ig or with anti-B7 mAbs) will continue to be an important focus of clinical studies.

h1F1 and h3D1 are humanized anti-B7.1 (CD80) and B7.2 (CD86). The DNA encoding the complementarity determining regions from the murine antibodies were molecularly spliced on to the DNA for the human kappa light, and the DNA for the $\gamma 2$ heavy chain sequences mutagenized to minimize Fc binding.*In vitro* h1F1 and h3D1 were shown to block CD28-dependent T-cell proliferation and decrease mixed lymphocyte reactions. In nonhuman primate models, h1F1 and h3D1 were able to delay renal allograft rejection, and their effectiveness was not undermined by the use of calcineurin inhibitors or steroids (30). The monoclonal antibodies need to be used in tandem, since either B7.1 or B7.2 is sufficient to stimulate T cells via CD28. A single phase I study in renal transplant recipients was performed in patients receiving maintenance therapy consisting of cyclosporine, mycophenolate mofetil and steroids. Patients received a single pretransplant dose ranging from 0.15 mg/kg to 5 mg/kg. Though the results of the study are yet to be published, the preliminary results appear to show that these monoclonal antibodies were safe and effective. While Wyeth Pharmaceutical at the present time has decided not to proceed with further development of these antibodies, they may yet emerge in the future through licensing agreements.

LEA29Y is a second-generation CTLA4Ig (extracellular domain of CTLA4 and IgG1 Fc domain) with an increase in binding avidity to CD80 (2-fold) and CD86 (4-fold), and approximately 10-fold more effectiveness*in vitro* than CTLA4Ig on a per dose basis in inhibiting T-cell effector functions. A phase I/II trial is currently underway in primary renal transplants with an immunosuppression regimen based on preclinical studies performed by Drs Chris Larsen and Tom Pearson at Emory

University (unpublished results). In the phase I study, 210 primary renal transplant patients are randomized to three treatment groups, group 1 and group 2 are treated with different regimens of LEA29Y, basiliximab (20 mg day 0 and day 4), mycophenolate mofetil 2 g and conventional steroid therapy. Patients randomized to group 3 serve as controls and are treated with a standard regimen consisting of basiliximab (20 mg at day 0 and day 4), cyclosporine, mycophenolate mofetil, and steroids. Patient enrollment in this trial should be completed by December 2002. This study may provide an important clue to the clinical efficacy achieved by blocking a single tract of the costimulatory pathway. It is possible, though, that effective clinical blockade of the costimulatory signal may require disruption of several targets within the pathway (29).

Inhibitors of T-cell activation and signaling

T-cell receptor (TCR)-coupled signaling in addition to costimulation delivered by CD28 activation results in activation of a number of signaling pathways that ultimately culminate in T-cell activation and cytokine production (31). Pre-clinical and *in vitro* inhibitors of signaling protein kinases for Lck, ZAP-70, PKC-θ, as well as MAPK cascade, are available. ZAP-70 inhibitors are particularly interesting in view of ZAP-70 s selective expression in T lymphocytes and natural killer cells. Inhibitors of the calcium-release-activated Calcium channel (CRAC) as well as specific inhibitors of NFAT (nuclear factor of activated T cells) rather than the phosphatase calcineurin may also be effective targets for inhibiting T-cell activation. Whether any of these agents will be developed clinically depends on a variety of factors, including imparting bioactivity and selectivity to these small molecules *in vivo*.

Inhibitors of T-cell proliferation

Effective T-cell activation requires T-cell proliferation. The new anti-interleukin-2 α chain receptor monoclonal antibodies cannot completely block T-cell proliferation as proliferative signals may occur through the intermediate affinity interleukin 2 receptor β γ or through pathways that involve cytokines other than IL2. The current approaches to blocking T-cell expansion are the disruption ofcytokine signaling or the inhibition of nucleotide incorporation required for cellular proliferation. Signaling through the γ chain requires activation of the Janus protein tyrosine kinase, JAK3, which also mediates signals from receptors for IL4, IL7, IL9 and IL15. Since JAK3 is required for the transduction of proliferative signals, inhibitors of JAK3 can be potentially powerful and useful drugs in transplantation (32). Individuals genetically lacking JAK3 have severe immunodeficiency disease (33). Whether JAK3 inhibitors turn out to be prohibitively immunosuppressive remains to be determined. Several JAK3 inhibitors, including one from Pfizer Pharmaceuticals, are development candidates for transplantation.

Novel antimetabolites include Lilly's Gemcitabine, a pyrimidine synthesis inhibitor currently being tested in a miniature swine model for renal transplantation, and FK778. FK778, a new oral immunosuppressive agent under development by Fujisawa Healthcare Inc., is an analog of the active metabolites of leflunomide (34). FK778 has a unique mechanism of action, binding to dihydro-orotate dehydrogenase and inhibiting de novo pyrimidine biosynthesis, thereby blocking T- and B-cell proliferation and strongly suppressing IgM and IgG antibody production. In addition, FK778 appears to have antiviral effects, including the polyoma virus. FK778 is currently in a phase II trial in Europe. A new, rationally designed inhibitor of inosine monophosphate dehydrogenase, VX-497, with a mechanism of action similar to mycophenolate mofetil, has been developed by Vertex and used in clinical studies in patients with psoriasis and hepatitis C. Despite encouraging preclinical studies in renal transplantation in dogs, however, its clinical development in transplantation remains in doubt.

Inhibitors of Lymphocyte Trafficking and Chemokine Receptor Blockade

FTY720 is a synthetic structural analog of myriocin, a metabolite of an ascomycete. FTY720 shares structural and functional homology with sphingosine-1-phosphate (S1P), a natural ligand to several G-protein-coupled receptors. FTY720 displays a novel mechanism of action characterized by sequestering of lymphocytes into secondary lymphoid organs without affecting their functions or properties (35). FTY720-monophosphate (FTY720-P), the active form of the drug, acts as an agonist and signals the S1P receptor family, $S1P_4$ and $S1P_5$ on lymphocytes, thereby increasing the intrinsic mobility of the cells and their responsiveness to chemokines (36,37). Thus the FTY720P-triggered lymphocytes are sequestered to sites of high constitutive homing chemokine expression, namely lymph nodes and Peyers patches. The sequestration to the lymphoid system reduces migration of effector cells to inflammatory tissues and graft sites. In a recently published study, 20 stable renal transplant recipients on a cyclosporine-based regimen were treated with single oral doses of FTY720 ranging from 0.25 to 3.5 mg (38). FTY720 was well tolerated with no serious adverse events, except for transient asymptomatic bradycardia in 10/24 doses. The elimination half-life ranged from 89 to 157 h independent of dose. FTY720 pharmacodynamics were characterized by reversible transient lymphopenia within 6 h, the nadir being 42% of baseline. The lymphocyte count returned to baseline within 72 h in all dosing cohorts except the highest. The interim results of two FTY720 trials were reported at the 2002 ATC meeting in Washington DC (39,40). The first study assessed the efficacy of four different maintenance doses of FTY720 (0.25 mg, 0.5 mg, 1 mg, 2.5 mg) in 155 patients concomitantly treated with cyclosporine and prednisone (39). The incidence of acute rejection ranged from 38% to 11%. The second trial was performed in patients at risk for delayed graft function and the immunosuppression regimen consisted of FTY720 2 mg, RAD 2 mg and prednisone (40). Fifty-six patients were enrolled in this study, with a reported rejection rate of 19% (mean follow-up 176 days). Both trials have stopped enrollment following several episodes of severe bradycardia (probably mediated by activation

of S1P receptors on atrial myocytes). New phase II and phase III trials are being considered for initiation in 2003. FTY720 appears to be an excellent candidate for rational drug design to eliminate its side-effects.

Chemokines play an important role in rejection by virtue of their critical role as regulators of trafficking and activation of lymphocytes (41,42). The receptors for chemokines are G-protein-coupled receptors expressed on a variety of leukocytes. Studies using targeted disruption of specific chemokine receptors, whether with receptor knock-out models, or receptor blockade with antagonists or monoclonal antibodies, have resulted in prolongation of allograft survival in experimental animals(42–46). These approaches appear to be more effective than neutralizing the cytokines with antibodies. Of approximately 18 chemokine receptors, at least three appear to play important roles in rejection in experimental models: CCR1, CXCR3, CCR5 (42,44,45). In experimental studies the chemokine receptor antagonists are more effective when used with low-dose calcineurin inhibitors than when administered as monotherapy. Development programs are currently in place for antagonists of CXCR3 and CCR1. While transplantation may not be the first indication in the clinical development of these agents, it is clear from experimental models that blockade of chemokine receptors could become an important addition to the therapeutic armamentarium in the prevention of rejection.

Conclusion

The next decade holds the promise of delivering newer, safer and more effective therapies to prevent acute and chronic rejection in organ transplantation. A pharmacologically promoted state of antigen-induced tolerance may even finally be achieved. In the interim, with no prospects for new drugs, transplant physicians should continue to experiment with immunosuppressive regimens, using currently approved drugs and biologic agents to minimize toxicities and improve long-term outcomes.

Acknowledgments

The author would like to acknowledge Peggy Millar for the preparation of the manuscript and for designingFigure 1. Dr Vincenti received research grants from Roche Pharmaceuticals, Wyeth Pharmaceuticals, Novartis Pharmaceuticals, Bristol-Myers Squibb, Fujisawa Healthcare and Xoma.

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